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EDITORIAL COMMENT

A Twist in Our Understanding of Enzyme Elevation After Coronary Intervention*

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Central to our understanding of acute myocardial infarction (MI) is the tight relationship between myonecrosis and the presence of elevated serum levels of certain enzymes known to originate from within myocardial cells. Together with presence of either chest discomfort or typical electrocardiographic (ECG) changes, an elevation in cardiac enzymes confirms the diagnosis of acute MI. Recently, even more emphasis has been placed on the significance of the role of serum enzymes. One publication revising criteria for acute MI indicates that the isolated finding of enzyme elevation in the setting of a percutaneous coronary intervention (PCI) is sufficient for the diagnosis of acute MI (1). This change in definition has major implications when gauging the risk/benefit ratio of PCI, especially in comparison with alternative treatment options.

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The association between PCI and subsequent detection of elevated levels of creatine kinase (CK), and in particular its MB isoenzyme (CK-MB), is well documented (2). Enzyme elevations are more common when balloon angioplasty is supplemented by additional procedures such as atherectomy or stent implantation (3–5). The greater potential for these adjunctive therapies to cause atheroembolism with subsequent impairment of microvascular function may explain this relationship (6). Approximately half of instances of CK-MB elevation during PCI are associated with chest pain syndromes, new ECG abnormalities, or other events (e.g., abrupt closure, side branch occlusion, or slow coronary flow), and there is agreement that such occurrences can be considered as legitimate adverse events (7).

More controversial has been the significance of elevations of CK-MB after PCI in asymptomatic patients who appear to have had an uncomplicated and successful procedure. Are such patients experiencing true MIs in the classic sense, and if so, are the consequences of these infarctions similar to those that occur spontaneously? On one hand, certain data indicate that asymptomatic CK-MB elevations are associated with an increased risk of late, adverse clinical events. One report indicates that for PCI of aortocoronary saphenous venous grafts, CK-MB elevations, even in an otherwise uncomplicated procedure, are associated with late mortality (8). A similar relationship between apparently uncomplicated elevations of cardiac enzymes and outcome may exist for native coronary arterial PCI when CK-MB elevations are excessive, that is, >8 times normal (5). In addition, one investigation using a contrast-enhanced magnetic resonance imaging technique suggests that even mild elevations of CK-MB are associated image-detectable sites of myocardial injury (9). On the other hand, a comparative analysis indicates that the development of a Q-wave on the ECG is associated with a far greater risk of late death than even large isolated elevations in CK-MB (5). Also, milder elevations in the 1 to 5× range may not be associated with procedural, in-hospital, or late adverse events (4,7), although not all agree on this finding (10,11). Importantly, the prevalence of such events may actually become more common because troponin T and troponin I appear to be more sensitive markers than CK-MB (12,13).

The relationship between enzyme elevation and outcome is of special importance given the well-documented ability of glycoprotein IIb/IIIa antagonists to reduce the magnitude and frequency of enzyme elevations among patients having PCI (14–16). Routine administration of these agents, however, incurs substantial financial expense and an increased risk of procedure-related hemorrhage that in certain instances can be serious or fatal (17).

The report by Iakovou et al. (18) in this issue of the *Journal* adds another twist in our effort to understand the significance of elevations in cardiac enzymes associated with the use of intracoronary stents. Most coronary lesions treated by balloon angioplasty also are stented. This practice is based on the recognition that routine stent use is associated with a lower likelihood of abrupt artery closure, in-hospital MI, restenosis, and repeat revascularization by either repeat PCI or coronary bypass surgery. Also well acknowledged is the inverse relationship between stent cross-sectional area at deployment and the likelihood of developing in-stent restenosis. In other words, the larger the stent area, the less is the chance for lesion recurrence within the stent. This relationship is especially valid for bare metal stents and to a lesser degree for sirolimus-eluting stents (19). Iakovou et al. (18) confirmed this relationship in a cohort of 989 consecutive patients who had intravascular ultrasound as part of their stent implantation procedure. Patients whose stent area exceeded that of the arterial lumen area had the lowest incidence of target lesion revascularization at one year of follow-up. Conversely, patients in the group with the lowest stent area had the highest rate of restenosis. A second finding was that a step-wise relationship in the magnitude of peak periprocedural CK-MB levels was observed according to the degree of stent expansion. Thus, the proportion of patients experiencing mild or

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marked elevations in CK-MB was least among the group with under-expanded stents and greatest among those with optimal stent expansion. Patients with intermediate stent expansion had enzyme findings that fell between the two other groups.

At first glance, each of these findings appears straightforward and consistent with our background knowledge of PCI and enzyme response. Optimal stent outcome, in terms of avoiding restenosis, means aggressive initial stent expansion achieved by high-pressure balloon inflations. This strategy, however, carries with it the risk of incremental distal atheroembolization, myonecrosis, and enzyme elevation. Continuing this reasoning, one would expect to observe a greater incidence of adverse events during the course of follow-up among the optimal stent group. This, however, was not the case. Paradoxically, the incidences of in-hospital death, Q-wave MI, and emergency bypass surgery were similar and low among the three groups. For example, although more than half of the patients in the optimal stent deployment group had elevations of CK-MB, only 1% had Q-wave MI, and only 0.2% died during the hospitalization. Even at one year of follow-up, there were no differences in the cumulative rates of Q-wave MI or death. In fact, the lowest mortality rate was among the optimal stent (highest CK-MB) group.

Before attempting to interpret the findings of this provocative study, we must address certain questions. First, are the observations really correct? Is there indeed no added risk of adverse late clinical events from aggressive stent expansion and associated increased incidence of myonecrosis? If the investigation were repeated with different patients at different sites, would there still be no difference in one-year mortality? These questions cannot be answered directly. However, it is possible that the groups in this report were too small to detect true differences or that there was an imbalance of selected characteristics at baseline, for example, impaired renal function, that could influence late mortality.

Second, is it possible that optimal stent expansion confers benefits beyond in-stent restenosis that offset the deleterious influence of myonecrosis? For instance, more robust stent deployment may lower the chance for stent thrombosis, a complication that can result in MI and death.

Third, was the length of follow-up in this report sufficient time to detect the effect of subtle differences in myonecrosis on mortality? Perhaps the rates of adverse events at five years will differ from those at one year.

Fourth, in the era of drug-eluting stents, will the criteria for achieving "optimal" stent deployment change? Will it be necessary for stent cross-sectional area to match or exceed lumen cross-sectional area? Although data to answer this question are limited at present, at least one investigation suggests that smaller stent cross-sectional areas are acceptable if sirolimus-eluting rather than bare-metal stents are used (20). If true, more modest deployment inflation pressures with less lesion barotrauma may diminish the frequency and magnitude of cardiac enzyme elevations.

In the final analysis, it appears clear that PCI-related elevations in cardiac enzymes are frequent and are statistically associated with less favorable late outcomes. Even if unassociated with other peri-procedural adverse clinical events, isolated enzyme elevations carry some risk. For patients receiving stents, however, these potential deleterious influences appear to be of insufficient magnitude to offset the beneficial effects of optimal stent deployment when measured by important, late clinical events.

In addition, the findings of this investigation have implications that extend beyond its immediate objective. Those who classify isolated enzyme elevations during PCI as being equivalent to spontaneous ST-elevation infarction due to proximal coronary occlusion should take note. Although both events may reflect myonecrosis, they differ substantially in their consequences and should be considered as distinctly different events, particularly when making formal comparisons of therapeutic options.

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